Project Details	
Project Code	NMH27Ca Massey
Title	Power Failure: Why Neurons Die in Huntington's Disease
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	Huntington's disease is an inherited brain disorder that causes progressive movement, cognitive and sleep problems, yet there is still no effective treatment. This PhD project asks why vulnerable neurons die, focusing on the link between DNA damage, PARP signalling, mitochondrial failure and metabolic collapse. The student will combine cutting-edge Drosophila genetics, human stem cell-derived neurons, DNA damage assays, sequencing approaches, live-cell imaging and metabolomics to uncover disease mechanisms and test therapeutic strategies. Based at Cardiff University, the student will join the collaborative Cardiff University, GW4 and UK Dementia Research Institute research communities, receiving outstanding multidisciplinary training.
Description	Huntington's disease (HD) is a progressive neurodegenerative disorder characterised by worsening motor dysfunction, psychiatric symptoms and cognitive decline, ultimately leading to dementia and premature death. There is currently no disease-modifying treatment. HD is caused by a CAG repeat expansion in the HTT gene, yet despite its simple genetic basis, we still do not understand why specific neurons are particularly vulnerable to degeneration. DNA damage, somatic repeat instability, mitochondrial dysfunction and metabolic failure are all recognised features of HD, but how these processes interact to drive neuronal death remains unclear. This project is based on the hypothesis that mutant huntingtin promotes DNA damage and genome instability, triggering maladaptive DNA damage responses such as excessive PARylation. This depletes NAD+, disrupts glycolysis and mitochondrial metabolism, increases oxidative stress and ultimately drives neuronal dysfunction and death. Our preliminary data demonstrate that DNA repair genes, including parp, mlh1 and msh6, strongly modify HD phenotypes in Drosophila, suggesting that the balance of DNA repair pathways is critical for neuronal survival. Using complementary Drosophila and human iPSC-derived neuronal models, this project will define how DNA damage and repair intersect with mitochondrial dysfunction and metabolism to drive HD pathology, identifying potential therapeutic targets. Dr Thomas Massey and Dr Mariah Lelos will provide expertise in HD biology, human iPSC models and clinical translation, while Dr Gaynor Smith's laboratory will contribute strengths in Drosophila neurodegeneration, mitochondrial biology, advanced imaging and omics. Professor James Hodge (University of Bristol) will provide specialist training in Drosophila behavioural, sleep and circadian neuroscience. Aim 1. Define how DNA damage pathways modify Huntington's disease in vivo The student will use established Drosophila models expressing pathogenic human HTT to determine whether DNA damage and repair pathways are causal drivers of neuronal degeneration. Priority DNA repair genes will be manipulated using RNAi, CRISPR-based approaches

	and available mutant lines. Phenotypic analyses will include lifespan, locomotor performance, sleep, neurodegeneration, neuronal integrity and huntingtin aggregation. DNA damage will be assessed using complementary assays, including γ-H2Av, PARylation, 8-oxodG immunostaining and comet assays. DNA repair activity will be quantified using EdU incorporation in ex vivo fly brains. Where increased repair activity is detected, sequencing-based approaches will be used to map repair events across the genome. Genetic and pharmacological PARP inhibition will determine whether restoring DNA damage signalling improves neuronal function. Student ownership: The student will prioritise candidate DNA repair genes, optimise genetic interaction studies, select reporter lines and determine which candidates progress to mechanistic investigation. Aim 2. Test whether DNA damage drives mitochondrial dysfunction in human HD neurons Mechanisms identified in flies will be tested in human iPSC-derived cortical neurons generated using our established inducible neuronal differentiation system. The student will quantify DNA damage, PARylation, mitochondrial morphology, membrane potential, oxidative stress, respiration and neuronal survival. DNA damage will be measured using γ-H2AX, 8-oxodG and comet assays, with sequencing approaches incorporated where appropriate. Mitochondrial function will be assessed by TOMM20 imaging, live-cell mitochondrial probes, TMRM, mitoSOX, Seahorse analysis of oxidative phosphorylation and glycolysis, together with measurements of NAD+, NADH and ATP. The student will determine whether genetic or pharmacological modulation of PARP signalling rescues mitochondrial dysfunction and restores cellular bioenergetics. This provides a clear translational pipeline in which discoveries from in vivo genetics are validated in human neurons and assessed for therapeutic potential. Student ownership: The student will prioritise the most informative cellular phenotypes, optimise imaging and metabolic assays, and select the most promising DNA repair and PARP interventions for validation. Aim 3. Define the metabolic consequences of DNA damage and PARP activation PARP activation consumes NAD+, leading to ATP depletion, impaired glycolysis and mitochondrial dysfunction, suggesting that parthanatos contributes to metabolic failure in HD. To define this pathway, the student will combine genetic approaches with pharmacological inhibition of key parthanatos components, including the clinically approved PARP inhibitors olaparib, niraparib and veliparib, together with the brain-penetrant PAAN/MIF inhibitor PAANIB-1. Targeted metabolomic analyses will be performed in Drosophila brains and human neurons to determine how mutant HTT and DNA damage signalling reshape metabolism. Initial analyses will quantify NAD+, NADH/NADPH and ATP before progressing to unbiased mass spectrometry-based metabolomics where appropriate. Dysregulated metabolites will be mapped onto metabolic pathways, and conserved enzymes and metabolic nodes will be prioritised for functional validation

	using complementary genetic and pharmacological approaches across both model systems. Student ownership: The student will lead metabolite validation by selecting the most informative biochemical, imaging and functional assays to confirm key metabolic changes and prioritise candidate therapeutic targets.
Can be completed part time?	No
Supervisory Team	
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